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(54) Title: CO-ADMINISTRATION OF CG250 AND IL-2 OR IFN-ALPHA FOR TREATING CANCER SUCH AS RENAL CELL CARCINOMAS

(57) Abstract: A method for enhancing the therapeutic effect of cytokine treatment is disclosed. More specifically the present invention relates to a method for administering to a tumor patient a therapeutic dose of cytokine in combination with antibodies directed against the tumor associated antigen carbonic anhydrase IX (CAIX/G250/MN). The improved treatment method is characterized in a significantly reduced cytokine-related toxicity combined with potentiated effectiveness of anti-G250 antibody alone, resulting in a positive therapeutic response with respect to that observed with single anti-tumor agents alone.

CO-ADMINISTRATION OF CG250 AND IL-2 OR IFN-ALPHA FOR TREATING CANCER SUCH AS  
RENAL CELL CARCINOMAS

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**Description**

10 The invention relates to a method for the treatment of malignant disorders, particularly renal cell carcinoma (RCC), comprising the coadministration of low-dose cytokine, particularly IL-2 or IFN- $\alpha$ , and an antitumor antibody.

15 It is estimated that 30,000 new cases of renal cell carcinoma (RCC) were diagnosed in the United States in 1999, with 11,900 deaths resulting from the disease (1). Estimates of new cases that have overt metastatic disease at the time of diagnosis range from 25% to 40% (2;3). Prognosis for these 20 patients is bleak, with a median survival of 10 months. For the remaining cases in which the disease appears to be localized, the treatment of choice is radical nephrectomy. However, one third of these patients will later manifest metastatic disease and ultimately die from their cancer.

20

25 To date chemotherapy has not demonstrated sufficient anti-tumor activity to prolong the survival of patients with metastatic disease (4;5). Single agent or multiple agent chemotherapy has not demonstrated a response rate greater than 10-15%. Due to less than satisfactory responses to chemotherapy and surgery, and to the indirect evidence that host immune mechanisms play a significant role in the natural history of RCC, there is a continued exploration of immunotherapy in this disease (6-8). Interferon-alpha (IFN- $\alpha$ ) and interleukin-2 (IL-2) have indeed shown 30 anti-tumor activity in approx. 20% of patients (9-13), but this was often associated with severe toxicity.

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Interleukin-2 (IL-2) is an immune system stimulating agent that can enhance proliferation and activation of T cells, NK cells and LAK cells and can induce the secretion of a variety of cytokines including IL-6 and interferon alpha (IFN- $\alpha$ ) and gamma (IFN- $\gamma$ ). Initial administration of IL-2 causes a transient disappearance of lymphocytes from the vascular compartment with a rebound after 24-48 hrs. After prolonged administration an expansion of various types of white blood cells is seen. IL-2 has been extensively investigated as an immune therapeutic for cancer and was shown to have activity against melanoma and renal cancer (6,8). High dose IL-2 therapy has been approved by FDA for the treatment of advanced renal cell carcinoma. The dosing scheme consists of an intravenous bolus of 0.6-0.7 MIU/kg every 8 hrs, repeated until further therapy is limited by toxicity (18). A treatment course consists of two cycles of therapy separated by 7-10 days. In each cycle patients may receive 10-14 doses of IL-2. The overall response rate is 15% with 5% complete responses.

There is considerable toxicity related to this high dose IL-2 treatment, requiring uptake in an intensive care unit. A sepsis-like syndrome with hypotension requiring pressor support as well as a systemic vascular leakage leading to respiratory distress can occur. Other toxicities/side effects are cardiac arrhythmia, fluid retention, fever, headache and mental confusion, elevation of liver enzymes, nausea and vomiting, thrombocytopenia, hyper/ hypothyreoidism, and pruritus (18). Due to the high toxicity profile alternative dosing schemes have been developed, such as low dose iv and sc treatment, aiming at reducing toxicity while retaining efficacy. In general it can be stated that these low dose treatments indeed are far less toxic (19-22). Generally, this low-dose IL-2 treatments, however, do not show any substantial efficacy.

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The antibody G250 recognizes the tumor-associated antigen carbonic anhydrase IX (CAIX/G250/MN), present on more than 75% of renal cancers. The reactivity with normal tissues is restricted to the gastric epithelium and the biliary ducts in the liver (14;15). Phase I/II trial of the 5 murine G250 antibody with  $^{131}\text{I}$  labeling for radioimmunotherapy has been completed and the results have been published (16). A chimeric G250 antibody constructed from a mouse Fv region with a human IgG1 kappa Fc region (15) has been shown to be equivalent to the murine G250 antibody in competitive combining assays. The chimeric antibody was labeled with 10  $^{131}\text{I}$  and used for diagnostic study in RCC patients (17).

The administration of a combination of cytokines and therapeutic antibodies has been described (24, 25, 26, 27, 28; US 5,104,652 and 15 WO 01/87336. There have been different schemes for the administration of antibody and cytokine combinations, which, however, have generally not shown the desired synergic effects and finally remained unsuccessful. Most of the IL-2 treatment protocols comprise an intermittent short-term administration of IL-2 in order to reach a reduction of the side effects.

20 Liu et al. (Cancer Immunol Immunother 51 (2002), 171-177) describe a cytokine enhancement of ADCC by administration of chimeric G250 antibody *in vitro*. According to the authors, these results suggest that a combination immunotherapy of chimeric G250 antibody with cytokines such as IL-2 might show promise in the treatment of RCC.

25 An abstract of Beck et al., Proceedings of the American Association for Cancer Research, Vol.43, (March 2002) describes a phase I/II trial with monoclonal antibody G250 in combination with low dose IL-2 in metastatic RCC. In phase I, patients received G250 once weekly i.v. and IL-2 s.c. 30 according to an alternating low dose and periodic pulsing treatment scheme over 6 weeks (1.8 MIU or 5.4 MIU IL-2 per day, single dose). During phase II, six patients continued to receive treatment for another 6

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weeks and nine additional patients were enrolled for a 12-week treatment. While the treatment was tolerated well, 4 of 14 patients showed stabilization of initially progressive disease. One of these four showed a partial remission when seen for the follow up in week 34. An additional 5 patient had a partial remission first observed in week 16, this response was last confirmed in week 34.

The object underlying the present invention was to provide a treatment protocol for coadministering an anti-tumor antibody and a low dose 10 cytokine which is more efficient than previous protocols without causing substantive side effects.

According to the present invention, a novel method for the treatment of a malignant disorder is provided, comprising coadministering an anti-tumor 15 antibody and a cytokine, wherein the cytokine is administered continuously or repeatedly, preferably daily in a low dose form.

A further embodiment of the present invention relates to a method for the treatment of a malignant disorder, comprising:

20 a) first treatment stage comprising administering a low-dose cytokine, preferably a continuous or repeated administration of a low-dose cytokine, and

25 b) a second treatment stage comprising coadministering an anti-tumor antibody and a low-dose cytokine, wherein the cytokine is preferably administered continuously or repeatedly.

According to the present invention, the cytokine is administered in a low- 30 dose form, wherein the administration preferably occurs continuously or repeatedly over the whole therapy interval. The administration is preferably daily each second day, and/or three times a week. By means of this

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continuous/repeated low-dose administration, the cytokine level is sufficiently high to increase the activity of the anti-tumor antibody, e.g. by increasing ADCC and/or to activate the immune system of the patient, e.g. the NK cells without causing substantial side effects, particularly cytokine-related toxicity. Compared to an administration of the anti-tumor antibody or the cytokine alone, the therapeutic efficacy of the combined administration is increased by more than 15%.

The administration of "low-dose cytokine" according to the present invention means that the cytokine is administered in a dose which is pharmaceutically effective in improving the efficacy of an antibody therapy in the substantial absence of toxic side effects, e.g. in the substantial absence of grade 3 or higher of National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Version 2.0, April 1999, more preferably in the substantial absence of grade 2 or higher and most preferably in the substantial absence of grade 1 or higher.

The cytokine is preferably selected from the group consisting of interleukins, e.g. IL-2,3,4,5,6,7,8,9,10,11,12,13,14 and 15, interferons e.g. IFN- $\alpha$ , IFN- $\beta$  and IFN- $\gamma$ , TNF- $\alpha$ , TNF- $\beta$ , nerve growth factor (NGF), ligands of CD 40, FAS, CD 27 and CD 30, macrophage-inhibiting protein, Rantes, active fragments and pharmaceutically acceptable analogues and derivatives thereof and mixtures thereof. More preferably, the cytokine is selected from IL-2 and IFN- $\alpha$ . A preferred dosage of IL-2 in the range of 1 MIU to 10 MIU daily, particularly in the range of 1.5 MIU to 6 MIU daily. The preferred dosage of IFN- $\alpha$  is 1 to 10 MIU three times a week, particularly in the range of 1 to 4 MIU three times a week.

The cytokine dose may be constant during the whole treatment. Alternatively, the dose may be a variable dose, particularly in the second treatment stage of a two-stage protocol, i.e. the dose may be altered during the treatment between a first low dose and a second low dose,

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wherein the second low dose may be up to five times higher than the first low dose. For example, the first low dose may be given in the first week of treatment, e.g. in the second treatment stage of a two-stage protocol, and in the second week, the first and second dose are given alternatively. In 5 the third week, the administration is as in the first week, the fourth week, the administration is as in the second week and so on.

The cytokine may be administered subcutaneously or intravenously or in any combination thereof. The preferred administration is subcutaneously.

10

The second active ingredient of the therapy according to the present invention is an anti-tumor antibody. The term "anti-tumor antibody" according to the present invention relates to any antibody which has efficacy against a malignant disorder, particularly renal cell carcinoma. 15 Preferably, the antitumor antibody is directed against a so-called tumor antigen, i.e. an antigen, particularly a polypeptide or a carbohydrate structure which is associated with a malignant disorder such as specified above.

20

More preferably the antitumor antibody is selected from antibodies directed against the MN (G250) antigen. Antibodies against the MN antigen are for example described in EP-B-0 637 336. Especially preferable, the antitumor antibody is a chimeric or humanized G250 antibody or a fragment thereof. These antibodies may be produced by methods as described in 25 PCT/EP/02/01282 and PCT/EP/02/01283.

The antitumor antibody is preferably administered intravenously, e.g. by infusion or intravenous injection. The administration of the antitumor antibody is preferably in intervals of from 5-20 days, e.g. in intervals of 30 about 1 week.

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The whole treatment protocol of the invention preferably comprises time interval of from 50-200 days. If the treatment comprises a two-stage treatment, the first treatment stage preferably comprises 5-20 days, e.g. about one week and the second treatment stage preferably comprises 5-200 days, e.g. about 70-120 days.

Furthermore, the invention should be explained by the following examples.

#### **EXAMPLE 1**

10

#### **CLINICAL TRIAL COMPRISING COADMINISTRATION OF CHIMERIC G250 ANTIBODY (cG250) AND IL-2**

##### **1.1 Endpoint criteria**

15

###### **Primary endpoints**

**Toxicity**

**Objective tumor response**

###### **Secondary endpoints**

**ADCC**

**HACA**

**Time to progression**

**Overall survival**

20

25

##### **1.2 Design**

30

A prospective, open label, single arm, non-randomized phase I/II multicenter trial was carried out in patients with advanced renal cell cancer. In the phase I part of the study the first 6 patients received cG250 once weekly intravenously and IL-2 subcutaneously according to an alternating low dose (daily) and periodic pulsing treatment scheme for 6 weeks. After it was shown that the drug-related toxicity was acceptable

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according to defined criteria these 6 patients were treated for another 6 weeks for a total of 12 weeks and an additional 9 patients (start of the phase II part) were enrolled for a 12 weeks treatment. Patients showing objective response (CR, PR) or stable disease were offered an additional treatment cycle of 6 weeks.

5

The data base closure for the final analysis of all parameters except for

time of progression was the evaluation at week 22 for all patients. Further, the results of the long-term follow up for defining the time to progression of the objective responders and the stable disease patients were evaluated.

10

### **1.3 Study treatment, dosage and dosage regimen/administration**

15 cG250 was administered according to the treatment schedule in Table 1. Per dose 20 mg of the chimeric monoclonal antibody cG250 were given once a week (plus or minus two days) by intravenous infusion in 50-100 ml of normal saline for 11 consecutive weeks in total, preceded by a week of IL-2 alone. The infusion was administered over a period of 30 minutes.

20

IL-2 was administered subcutaneously according to the treatment schedule in Table 1. Subjects received or self-administered at home a single daily injection of commercially available recombinant human IL-2 for 12 consecutive weeks. Starting in week 1, patients received a single dose of 25 1.8 MIU sc IL-2 daily. In week 2 on day 1 the same amount of IL-2 was given preceded by cG250. The remaining days of week 2 patient received 1.8 MIU sc per day. In week 3 from day 1 to 3, patients received sc IL-2 pulsing with 5.4 MIU per day. On the remaining days IL-2 was given at 1.8 MIU. The IL-2 treatment of week 3 was repeated in week 5, 7, 9, and 11, 30 the scheme of week 2 in week 4, 6, 8, 10, and 12.

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In general the IL-2 injections were made early in the morning by the patient at home. Only on days of cG250 administration this injection was delayed until the patient was in the outpatient clinic. On the day of G250 application patients received IL-2 (irrespective of dose) one hour after the 5 G250 therapy.

#### **1.4 Test schedule and procedures/ Study Flow Chart**

10 The study procedures are described in detail in this section. A general overview of the tests and procedures of this protocol is given in the G250/IL-2 application scheme (Table 1).

15 Patients were closely monitored for safety reasons during the treatment period by weekly controls of vital signs, assessment of toxicity, Performance Status and laboratory tests, eg CBC, blood chemistry and radiological tests, if necessary. All blood drawings were performed before the administration of IL-2 and G250, respectively. The total volume of the blood drawings per patient in 5 months were about 300 ml.

20 The investigations/evaluations that were performed are listed in the following Table 1:

25

**Table 1: cG250/IL-2 application scheme**

cG250: iv infusion once weekly, given on day 1 of each week, outpatient clinic

IL-2: sc injection seven days/week, day 1 should be Monday or Tuesday,

30 outpatient clinic and at home

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	cG250	IL-2
Week 1	None	Day 1-7: 1.8 MIU per day single dose
Week 2	Day 1: 20 mg single dose	Day 1-7: 1.8 MIU per day
Week 3	"	Day 1-3: 5.4 MIU per day (pulsing scheme) Day 4-7: 1.8 MIU per day
5	Week 4	" As week 2
Week 5	"	As week 3
Week 6	"	As week 2
Week 7	"	As week 3
Week 8	"	As week 2
10	Week 9	" As week 3
Week 10	"	As week 2
Week 11	"	As week 3
Week 12	"	As week 2

15

### 1.5 Toxicity classification

Allergic reactions: Patients were removed from study for any grade  $\geq 2$  allergic toxicity according to NCI CTC toxicity scale.

20 Fever: Patients with  $> 39^{\circ}\text{C}$  fever (grade 2), but without allergic symptoms on the day of scheduled cG250 infusion did not receive cG250 until fever had dropped below  $38^{\circ}\text{C}$  (grade 0). If fever did not drop in 2

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days, the cG250 infusion was cancelled and treatment was resumed on the next scheduled G250 infusion date.

5 The sc injections of IL-2 were on days with fever > 39°C. The daily IL-2 injections were cancelled until fever has dropped below 38°C. In case the use of 500 mg paracetamol did not decrease the temperature below 38°C, the injection was suspended until the temperature is below 38°C again.

10 Pain, itching, erythema, swelling, inflammation, phlebitis and ulceration at the site of injection was considered as "local site reaction" according to the NCI CTC criteria; urticaria was diagnosed as part of "allergic reaction/hypersensitivity".

15 **1.6 ASSESSMENT OF EFFICACY**

**1.6.1 Efficacy parameters**

20 The objective response of the tumor was the main parameter of efficacy. The tumor evaluation was performed based on the WHO Tumor Evaluation Guidelines with 1) minimum size requirements for measurable target lesions and 2) tumor masses with clearly defined bi-dimensional measurements.

25 The tumor measurements for target lesions were performed with CT-scan or MRI scan. For all indicator lesions the minimum size of the largest tumor diameter was 1.0 cm.

30 All measurable lesions  $\geq$  1.0 cm up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, were identified as target lesions and recorded and measured at baseline.

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### **1.6.2 Methods of assessments (eg tumor response, specific tests)**

The tumor assessment was based on contrast medium-enhanced spiral computer-tomography (CT) or magnetic resonance imaging (MRI). The 5 same procedures were used throughout the study. All measurements were recorded in metric notation, using a ruler or calipers. All baseline evaluations were performed as closely as possible to the beginning of treatment and not more than 4 weeks before the beginning of treatment.

10 Tumor responses were evaluated according to the WHO criteria as follows:  
Complete response (CR): The disappearance of all known disease determined by two evaluations not less than four weeks apart.

15 Partial response (PR): 50% or more decrease in the sum of products of largest and perpendicular diameters of the lesions which have been measured to determine the effect of therapy by two evaluations not less than four weeks apart. In addition there can be no appearance of new lesions or progression of any lesion.

20 No change (NC) = Stable disease (SD): A greater than 50% decrease in total tumor size can not be established nor has a 25% increase in the size of one or more measurable lesions been demonstrated.

Progressing disease (PD): a 25% or more increase in the size of one or more measurable lesions, or the appearance of new lesions.

25

### **1.6.3 Timing of tumor evaluations**

30 Tumor evaluations were performed before study entry, at week 16 and 22 and for drop-outs at time of drop-out. The assessment in week 22 did serve to confirm the radiologic result seen in week 16.

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An effort was made to follow up all patients who are not progressing during their courses of treatment by performing CTs every 3 months after end of cG250 treatment. This served to assess the duration of the objective response or stable disease.

5

#### **1.6.4 ADCC assay**

The antibody-dependent cell-mediated cytotoxicity (ADCC) of isolated peripheral-blood mononuclear cells (PBMC) from patients was analyzed 10 using a <sup>51</sup>Cr release assay, according to Lamers et al. (29). Target cells were the SKRC MW1-cl4 (G250 antigen overexpressing RCC cell line). Controls were SKRC PBJ-cl1 (G250 antigen negative RCC cell line) and P815 (positive control with anti-P815 serum). After incubation with G250 and serial dilutions of PBMC of the patients the <sup>51</sup>Cr released by lysed 15 target cells was measured in the supernatant. The weighted mean of specific lysis of target cells was calculated.

### **1.7 STATISTICS**

20

#### **1.7.1 Methods / Analysis**

The study was based on a sequential enrollment of two groups of patients with a maximum of 30 evaluable patients enrolled. After enrolling 15 25 patients (stage 1) the study was continued enrolling the second group of 15 patients.

At the maximum enrollment number of 30 patients the trial was powered at 81% to detect an objective response rate of 15% against an assumed 30 spontaneous response rate of 5%.

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This trial design was chosen to minimize the expected enrollment of patients under objective and spontaneous response rates while maximizing the chances of early stopping at the interim analysis. The method of calculation was the Sequential Probability Ratio Test modified according to 5 Wald (30, 31).

The study size was based on  $\alpha \leq 0.05$  and  $1-\beta \geq 0.80$  to detect a difference between a spontaneous response rate of 5% versus an 10 underlying true response rate of 15%.

## 1.8 RESULTS

15 According to an internationally accepted definition (32), an objective response or disease stabilization for approximately at least six months after the disease being progressive at study entry is generally accepted as a "clinical benefit".

20 In the present study, approximately 30% of patients exhibited an objective response or a disease stabilization for 22 weeks or longer and therefore the above treatment schedule represents a "clinical benefit" for the treated patient group. A clinical benefit to such an extent has not been observed for this very problematic patient group (metastatic RCC patients, often in 25 the terminal stage of the disease).

Further, the treatment is safe. The combination treatment of i.v. administered cG250 and sc administered IL-2 was well tolerated. No 30 serious adverse events against cG250 were observed. Moderate adverse events typical for IL-2 treatment (and in most cases tolerable due to the low dose administration) and no allergic reactions and no human anti-chimeric antibody (HACA) reactions were observed.

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## EXAMPLE 2

### CLINICAL TRIAL COMPRISING COADMINISTRATION OF CHIMERIC G250 ANTIBODY (cG250) AND IFN- $\alpha$ .

5

The clinical trial was carried out as described in Example 1 except for the alterations in the administration protocol as shown in Table 2:

10

**Table 2: cG250/IFN- $\alpha$  application scheme**

cG250: iv infusion once weekly, given on day 1 of each week, outpatient clinic

IFN- $\alpha$ : sc injection 3 times per week, outpatient clinic and at home

15

	cG250	IFN- $\alpha$
Week 1	None	Day 1/3/5: 3 MIU single dose each
Week 2-12	Day 1: 20 mg single dose	Day 1/3/5: 3 MIU single dose each
20 For all patients with approved extension of treatment		
Week 17-22	Day 1: 20 mg single dose	Day 1/3/5: 3 MIU single dose each

25 The combination treatment of cG250 i.v. and IFN- $\alpha$  is s.c., was well tolerated. No serious adverse effects, related to cG250, were observed.

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Only moderate adverse events, typical for IFN- $\alpha$  treatment were found. These adverse events were well tolerable due to the low dose administration protocol. Further, no allergic reactions and no HACA-reactions were observed.

5

Preliminary results show the presence of a clinical benefit for the treated patient group.

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**Claims**

1. A method for the treatment of a cancer comprising co-administering an anti-tumor antibody and a cytokine to a subject in need thereof, wherein the cytokine is administered continuously or repeatedly in a low-dose form.
2. A method for the treatment of a cancer comprising co-administering an anti-tumor antibody and a cytokine to a subject in need thereof, wherein the method comprises:
  - (a) a first treatment stage comprising administering a low-dose cytokine, and
  - (b) a second treatment stage comprising co-administering an anti-tumor antibody and a low-dose cytokine.
3. The method of claim 1 or 2, wherein the low-dose cytokine comprises a dose which is pharmaceutically effective in the substantial absence of NIC CTC toxicity grade 3 or higher.
4. The method according to any one of claims 1-3 comprising a daily administration of a low-dose cytokine.
5. The method of any one of claims 1-4 wherein the cytokine is selected from interleukins and interferons.
6. The method of claim 5 wherein the cytokine is IL-2.
7. The method of claim 6 wherein the dose of IL-2 is in the range of from 1-10 MIU daily.
8. The method of claim 5 wherein the cytokine is IFN- $\alpha$ .

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9. The method of claim 8 wherein the dose of IFN- $\alpha$  is in the range of from 1-10 MIU three times a week.
10. The method of any one of claims 1-9 wherein the cytokine is administered in a substantially constant dose during the treatment.
11. The method of any one of claims 1-9 wherein the cytokine is administered in a variable dose during the treatment.
- 10 12. The method of any one of claims 1-11 wherein the cytokine is administered subcutaneously.
13. The method of any one of claims 1-12 wherein the antitumor antibody is selected from antibodies directed against the MN (G250) antigen.
- 15 14. The method of any one of claims 1-13 wherein the antitumor antibody is a chimeric or humanized G250 antibody or a fragment thereof.
- 20 15. The method of any one of claims 1-14 wherein the antitumor antibody is administered in intervals of from 5-20 days.
16. The method of claim 2 wherein the first treatment stage comprises 5-20 days.
- 25 17. The method of claim 2 wherein the second treatment stage comprises 50-200 days.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 03/06591A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61K39/395 A61K39/19 A61K38/20 A61K38/21

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BECK JOACHIM ET AL: "A Phase I/II trial with monoclonal antibody WX-G250 in combination with low dose interleukin-2 in metastatic renal cell carcinoma" PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, vol. 43, March 2002 (2002-03), page 910 XP008023397 93rd Annual Meeting of the American Association for Cancer Research; San Francisco, California, USA; April 06-10, 2002, March, 2002 ISSN: 0197-016X cited in the application abstract ---	1, 3-6, 10-17
Y	---	2 -/-

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- \*X\* document of particular relevance; the claimed Invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

- \*Y\* document of particular relevance; the claimed Invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

- \*&\* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

17 October 2003

27/10/2003

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## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 03/06591

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BLEUMER I ET AL: "A phase II trial with monoclonal antibody WX-G250 in advanced renal cell carcinoma" EUROPEAN UROLOGY SUPPLEMENTS, vol. 1, no. 1, January 2002 (2002-01), page 112 XP001164270 XVIIth Congress of the European Association of Urology; Birmingham, England, UK; February 23-26, 2002 ISSN: 1569-9056 abstract ---	2
X	LIU ZHANQI ET AL: "Anti-renal cell carcinoma chimeric antibody G250: Cytokine enhancement of in vitro antibody-dependent cellular cytotoxicity" CANCER IMMUNOLOGY IMMUNOTHERAPY, vol. 51, no. 3, May 2002 (2002-05), pages 171-177, XP001172419 ISSN: 0340-7004 cited in the application page 175, right-hand column, line 1 -page 176, left-hand column, line 31 ---	1,3-17
X	VAN DIJK J ET AL: "Therapeutic effects of monoclonal antibody G250, interferons and tumor necrosis factor, in mice with renal-cell carcinoma xenografts" INTERNATIONAL JOURNAL OF CANCER, vol. 56, no. 2, 1994, pages 262-268, XP008023392 ISSN: 0020-7136 page 263, right-hand column, paragraph 2 page 266, left-hand column, line 21 -page 267, right-hand column, line 4 ---	1-5,8-17
P,X	VARGA Z ET AL: "A prospective open-label single-arm phase II study of chimeric monoclonal antibody cG250 in advanced renal cell carcinoma patients." FOLIA BIOLOGICA (PRAGUE), vol. 49, no. 2, 2003, pages 74-77, XP008023418 ISSN: 0015-5500 abstract ---	1-17
		-/-

## INTERNATIONAL SEARCH REPORT

Internal Application No  
PCT/EP 03/06591

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>BLEUMER IVAR ET AL: "A phase I/II trial with chimeric monoclonal antibody WX-G250 in combination with low-dose interleukin-2 for patients with metastatic renal cell carcinoma."</p> <p>JOURNAL OF UROLOGY, vol. 169, no. 4 Supplement, April 2003 (2003-04), page 261 XP008023419</p> <p>98th Annual Meeting of the American Urological Association (AUA); Chicago, IL, USA; April 26-May 02, 2003</p> <p>ISSN: 0022-5347</p> <p>abstract</p> <p>-----</p>	1-7, 10-17

# INTERNATIONAL SEARCH REPORT

Intel

Application No.  
PCT/EP 03/06591

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  

Although claims 1-17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple Inventions in this International application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.